UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,662	12/27/2001	Eugene Herman	9195-081-999	7952

20583 7590 06/17/2004

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
SPIEGLER, ALEXANDER H	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 06/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/033,662	HERMAN ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *1-7 and 13-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/25/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. After further consideration, a new restriction requirement has been set forth below.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

1. Claims 1-7 (in part), drawn to methods of screening or identifying a subject at risk of developing Cardiac Response using 2D electrophoresis, classified in class 204, subclass 456, for example.
2. Claims 1-7 (in part), drawn to methods of monitoring the effects of therapy administered in a subject using 2D electrophoresis, classified in class 204, subclass 461, for example.
3. Claims 8-12 (in part), drawn to drawn to methods of screening or identifying a subject at risk of developing Cardiac Response using proteins, classified in class 435, subclass 7.1, for example.
4. Claims 8-12 (in part), drawn to methods of monitoring the effects of therapy administered in a subject using proteins, classified in class 514, subclass 2, for example.
5. Claims 13-17, drawn to proteins and kits comprising said proteins, classified in class 530, subclass 350, for example.
6. Claims 18-24, drawn to antibodies and kits comprising said antibodies, classified in class 530, subclass 387.1, for example.
7. Claims 25-27, drawn to drawn to methods of treating Cardiac Response using a nucleic acid, classified in class 514, subclass 44, for example.

8. Claims 28-30, 41 and 43-44, drawn to methods of screening for agents that interact with a polypeptide, classification undeterminable; classification dependent on agent.

9. Claims 31-40, 42-44, 48 and 53, drawn to methods of screening agents that modulate expression or activity of a CRPI, classification undeterminable; classification dependent on agent.

10. Claims 45-47 (in part), drawn to methods of screening or identifying a subject at risk of developing Cardiac Response using an oligonucleotide probe, classified in class 435, subclass 6, for example.

11. Claims 45-47 (in part), drawn to methods of drawn to methods of monitoring the effects of therapy administered in a subject, classified in class 435, subclass 4, for example.

12. Claims 49-51, drawn to an agent that modulates activity, classification undeterminable; classification dependent on agent.

13. Claim 52, drawn to a method of treating or preventing comprising administering an agent that modulates activity, classified in classification undeterminable; classification dependent on agent.

Further Restriction

The claims of Groups 1-13 are drawn to a multitude of Cardiac Response Associated Features, Cardiac Response Associated Protein Isoforms, antibodies thereto and methods which use these compounds. Each of the different Cardiac Response Associated Features, Cardiac Response Associated Protein Isoforms, antibodies and methods of use are independent and

distinct because no common structural or functional properties are shared. Accordingly, these claims are subject to restriction under 35 U.S.C. § 121.

Upon election of one of Groups 1-13, Applicant is additionally required to elect a **single** Cardiac Response Associated Feature, Cardiac Response Associated Protein Isoform, or antibody. For example, Applicants could elect Group 3, and CPRI-1. This requirement is not to be construed as a requirement for an election of species, since each of the compounds is not a member of a single genus of invention, but constitutes an independent and patentably distinct invention.

2. The inventions are distinct, each from the other because of the following reasons:

A) Inventions 1-4, 7-11 and 13 are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the inventions are directed to methods having different method steps, starting materials, and goals. For example, Inventions 1 and 2 are unrelated because Invention 1 is drawn to methods of screening or identifying a subject at risk of developing Cardiac Response using 2D electrophoresis, whereas Invention 2 is drawn to methods of monitoring the effects of therapy administered in a subject; Invention 3 is drawn to drawn to methods of screening or identifying a subject at risk of developing Cardiac Response using proteins, whereas Invention 4 is drawn to methods of monitoring the effects of therapy administered in a subject using proteins; Invention 7 is drawn to methods of treating Cardiac Response using a nucleic acid; Invention 8 is drawn to methods of screening for agents that interact with a polypeptide, whereas Invention 9 is drawn to

methods of screening agents that modulate expression or activity of a CRPI; Invention 10 is drawn to methods of screening or identifying a subject at risk of developing Cardiac Response using an oligonucleotide probe, whereas Invention 11 is drawn to methods of monitoring the effects of therapy administered in a subject using an oligonucleotide probe; Invention 13 is drawn to a method of treating or preventing comprising administering an agent that modulates activity.

B) The inventions of Groups 5, 6 and 12 are patentably distinct because they are drawn to different products having different structures and functions. The polypeptide of Group 5 is composed of amino acids linked in peptide bonds and arranged spatially in a number of different tertiary structures including alpha helices, beta-pleated sheets, and hydrophobic loops (transmembrane domain). The antibody of Group 6 is composed of amino acids linked in peptide bonds and arranged spatially in a very specific tertiary structure that allows that antibody to specifically bind to particular regions, i.e., epitopes, of the encoded polypeptide. Further, antibodies are glycosylated and their tertiary structure is unique, where four subunits (2 light chains and 2 heavy chains) associated via disulfide bonds into a Y-shaped symmetric dimer. Contrarily, the agent of Group 12 does not have a specified structure. Furthermore, the products of Groups 5, 6 and 12 can be used in materially different processes, for example, the antibody of Group 6 can be used in an immunoassay, the polypeptide of Group 5 can be used to make fusion proteins with an enzymatic function, whereas the agent of Group 12 can be used in making a medicament for the treatment or prevention of Cardiac Response. Consequently, the reagents, reaction conditions, and reaction parameters required to make or use each invention are

different. Therefore, the inventions of Groups 5, 6 and 12 are patentably distinct from each other. (See MPEP § 806.04, MPEP § 808.01, unrelated inventions)

C) Inventions 5 and (1-2, 7, and 10-11) are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are not required one for the other in that the proteins of Group 5 are not required for the methods of Groups 1-2, 7, and 10-11. As such, the Inventions would require search in separate and non-overlapping areas, imposing an undue search burden upon the examiner if not restricted.

D) Inventions 5 and (3-4, 8-9 and 13) are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the proteins of Group 5 could be used in any of the methods of 3-4, 8-9 and 13, or in an entirely different manner, such as in a purification reaction or in making antibodies.

E) Inventions 6 and (1-4, 7-11 and 13) are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are not required one for the other in that the antibodies of Group 6 are not required for the methods of Groups 1-4, 7-11 and 13. As such, the Inventions

would require search in separate and non-overlapping areas, imposing an undue search burden upon the examiner if not restricted.

F) Inventions 12 and (1-4 and 7-11) are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are not required one for the other in that the agents of Group 12 are not required for the methods of Groups 1-4 and 7-11. As such, the Inventions would require search in separate and non-overlapping areas, imposing an undue search burden upon the examiner if not restricted.

H) Inventions 12 and 13 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the agents of Group 12 could be used the methods of Group 13, or in an entirely different manner, such as in a method of modulating activity.

3. Because these inventions are distinct for the reasons given above and have acquired a different status in the art as demonstrated by their different classification and recognized divergent subject matter and because inventions 1-13 require different searches that are not co-extensive, examination of these distinct inventions would pose a serious burden on the examiner and therefore restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Ann Chen on June 10, 2004 a provisional election was made ***with*** traverse to prosecute the invention of Group 3, claims 8-12 and CRPI-1.

Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-7 and 13-53 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

Applicants' Arguments Filed on March 15, 2004

Applicants' argue Groups 3 and 4 should be examined together because they are both drawn to methods of detecting Cardiac Response-Associated Protein Isoforms, they are classified in the same class and the same subject matter would be searched for both of these groups.

Applicants' argue Groups 1 and 2 should be examined together because they are both drawn to methods that use two dimensional electrophoresis to analyze test samples, they are classified in the same class and the same subject matter would be searched for both of these groups.

Applicants' argue Groups 5 and 6 should be examined together because Group 5 is directed to CPRIs (proteins) and Group 6 is directed to antibodies capable of binding to CPRIs.

Applicants' argue the Examiner should require an election of a single species, rather than require restriction to a species as the Examiner has done in the outstanding office action.

(See Applicants' response on pages 4-6)

Response to Applicants' Arguments

Applicants' arguments, with respect to Groups 3 and 4, have been considered, but are not persuasive for the following reasons. First, even though Groups 3 and 4 are classified in the same class, they are classified in different subclasses, which independently and distinctly distinguish them from one another. Second, inventions 3 and 4 are unrelated. Group 3 is specifically drawn to screening, diagnosis, or prognosis for determining the stage or severity of Cardiac Response in a subject, whereas Group 4 is drawn to monitoring the effects of therapy administered to a subject having Cardiac Response (which would, at least, require the step of administering therapy before detection of any Cardiac Response-Associated Protein Isoforms, and before monitoring any effect of therapy). Accordingly, because they are directed to methods having different method steps and goals, they are patentably distinct from one another.

Applicants' arguments, with respect to Groups 1 and 2, have been considered, but are not persuasive for the following reasons. First, even though Groups 1 and 2 are classified in the same class, they are classified in different subclasses, which independently and distinctly distinguish them from one another. Second, inventions 1 and 2 are unrelated. Group 1 is specifically drawn to screening, diagnosis, or prognosis for determining the stage or severity of Cardiac Response in a subject, whereas Group 2 is drawn to monitoring the effects of therapy administered to a subject having Cardiac Response (which would, at least, require the step of administering therapy before monitoring any effect of therapy). Accordingly, because they are directed to methods having different method steps and goals, they are patentably distinct from one another.

Applicants' arguments, with respect to Groups 5 and 6, have been considered, but are not

persuasive for the following reason. The inventions of Groups 5 and 6 are patentably distinct because they are drawn to different products having different structures and functions. The polypeptide of Group 5 is composed of amino acids linked in peptide bonds and arranged spatially in a number of different tertiary structures including alpha helices, beta-pleated sheets, and hydrophobic loops (transmembrane domain). The antibody of Group 6 is composed of amino acids linked in peptide bonds and arranged spatially in a very specific tertiary structure that allows that antibody to specifically bind to particular regions, i.e., epitopes, of the encoded polypeptide. Further, antibodies are glycosylated and their tertiary structure is unique, where four subunits (2 light chains and 2 heavy chains) associated via disulfide bonds into a Y-shaped symmetric dimer. Furthermore, the products of Groups 5 and 6 can be used in materially different processes, for example, the antibody of Group 6 can be used in an immunoassay, whereas the polypeptide of Group 5 can be used to make fusion proteins with an enzymatic function. Consequently, the reagents, reaction conditions, and reaction parameters required to make or use each invention are different. Therefore, the inventions of Groups 5 and 6 are patentably distinct from each other. (See MPEP § 806.04, MPEP § 808.01, unrelated inventions) Furthermore, these Groups are classified in different subclasses, which is evidence of their divergent subject matter, and field of search. Accordingly, the restriction requirement is maintained.

Applicants' argument, with respect to an election of species, has been considered, but is not persuasive for the following reasons. As stated in the restriction requirement, the requirement is not to be construed as a requirement for an election of species, since each of the compounds is not a member of a single genus of invention, but constitutes an independent and

patentably distinct invention. Each of the different Cardiac Response Associated Features, Cardiac Response Associated Protein Isoforms, antibodies and methods of use are independent and distinct, and are each members of a different genus of invention because no common structural or functional properties are shared between the inventions. Accordingly, the restriction requirement is maintained.

It is also noted, Applicants correctly point out that claims 31-40, 42-44, 48 and 53 are drawn to methods of screening agents that modulate expression or activity of a CRPI, and not VRPI, as inadvertently stated in the Restriction Requirement mailed on September 26, 2003.

Status of the Application

6. Currently, claims 1-53 are pending, Claims 8-12 are rejected herein, and Claims 1-7 and 13-53 have been withdrawn as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.

The Claims have been interpreted as being drawn to the elected CRPI (CRPI-1), and elected method (method for screening, diagnosis or prognosis of Cardiac Response in a subject, for determining the stage or severity of Cardiac Response in a subject, or for identifying a subject at risk of developing Cardiac Response). Applicants should amend the claims to reflect the elected CRPI (CRPI-1).

Information Disclosure Statement

7. The information disclosure statement filed on April 25, 2003 complies with CFR 1.97, 1.98, and M.P.E.P. 609, and has been considered (see enclosed signed PTO-1449).

Specification

8. The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code throughout the specification. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 8-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 8-12 are indefinite because claim 8 is drawn to a method for screening, diagnosis or prognosis of Cardiac Response in a subject, for determining the stage or severity of Cardiac Response in a subject, or for identifying a subject at risk of developing Cardiac Response, however, the final step is for detecting, in a sample of serum from the subject, CRPI-1. The claims do not set forth the relationship between detecting CRPI-1 and a method for screening, diagnosis or prognosis of Cardiac Response in a subject, for determining the stage or severity of Cardiac Response in a subject, or for identifying a subject at risk of developing Cardiac Response. Therefore, it is not clear as to whether the claims are intended to be limited to a method of a method for screening, diagnosis or prognosis of Cardiac Response in a subject, for

determining the stage or severity of Cardiac Response in a subject, or for identifying a subject at risk of developing Cardiac Response or a method of detecting CRPI-1.

B) Claims 8-12 over "CRPI-1" because it is not clear as to what protein is being detected. The specification teaches that "CRPI" refers to:

> [A] protein isoform that is differentially present in a sample from a subject having a Cardiac Response compared with a sample from a subject free from any Cardiac Response or that is differentially present in a sample from a subject having one or more particular Cardiac Response compared with a sample from a subject free from such one or more particular Cardiac Response or having a distinct Cardiac Response. As used herein, a CRPI is "differentially present" in a first sample with respect to a second sample when a method for detecting the said feature... gives a different signal when applied to the first and second samples...A CRPI is characterized by one or more peptide sequences of which it is comprised...the CRPI may correspond to the previously-identified protein, be a variant of the previously identified protein, or be a previously unknown protein.

(see page 9, line 17 to page 10, line 11). This passage does not particularly point out and distinctly teach what is meant by "CRPI". That is, given this passage, the skilled artisan would not be able to clearly distinguish what a "CRPI" protein is. Furthermore, on page 45, Table IX, the specification shows that CRPI-1 has both a rat/mouse accession number and a human homologue accession number, and that CRPI-2 has the same rat/mouse accession number and a human homologue accession number as CRPI-1. Accordingly, given the lack of a clear definition in the specification of what "CRPI" is, and the differing accession numbers referred to as VRPI-1, it is not clear as to what specific protein is meant when referring to "CRPI-1".

C) Claims 9-12 are indefinite over "immunospecific" because it is not clear if the antibody will only bind to CRPI-1 and no other protein, or whether it can bind with CRPI-1 as well as other proteins. The specification does not define this recitation.

Claim Rejections - 35 USC § 112, 1st Paragraph (Enablement)

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 8-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

MPEP 2164.01 states:

> Even though the statute does not use the term 'undue experimentation,' it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)

The *Wands* court outlined several factors to be considered in determining whether a disclosure would require undue experimentation. These factors include, but are not limited to:

(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 1404.

In the instant case, the specification does not enable one of skill in the art to make and use the claimed invention for the following reasons:

(1) ***Nature of the Invention & Breadth of the Claims***

The claims are drawn to methods for screening, diagnosis or prognosis of Cardiac Response in a subject, for determining the stage or severity of Cardiac Response in a subject, and for identifying a subject at risk of developing Cardiac Response by detecting CRPI-1 in sample of serum from a subject.

The specification broadly defines "Cardiac Response" on page 7, lines 28-34, stating,

> "Cardiac Response" refers to and includes the activities and consequent alterations in cardiac function and other organ or cellular function and any condition that comes about from interaction of the heart with endogenous or exogenous effector agents, including xenobiotics, viruses or other biological agents, particularly those agents which are cardiotoxic, which can generate a cardiac response or which otherwise reduce or alter the function or physiological response of the heart.

This definition encompasses not only "activities" and "consequent alterations" in cardiac function and "other" organ or cellular function, but also "any" condition that comes about from interaction of the heart with endogenous or exogenous effector agents, including xenobiotics, viruses or "other biological agents". The specification does not specifically define what "activities" and "consequent alterations" are or what "activities" and "consequent alterations" can occur in cardiac function and "other" organ or cellular function. Furthermore, the specification does not define what "biological agents" are or what is encompassed by this recitation. Accordingly, the recitation of "cardiac response" is broadly drawn to encompassing any "activity" and "consequent alteration" in cardiac function (e.g., slowing, speeding up, or stopping of the heart beat, irregular heartbeat, deposition of amyloid on the heart, hardening of coronary arteries, narrowing of coronary arteries, etc.), and other organ or cellular function (encompassing numerous possible organs and cells effected), and any condition that comes about from interaction of the heart with endogenous or exogenous effector agents, including

xenobiotics, viruses or "other biological agents" (comprising a large plurality of possible interactions, xenobiotics, viruses or other biological agents).

Furthermore, the specification teaches,

> Cardiac response encompasses and includes those activities, alterations and physiological occurrences in the heart, or otherwise associated with the heart or the heart's function, which take place during any alteration of the heart including but not limited to any aspect or phase of aneurysm, angina, arrhythmia, cardiomyopathy (dilated, hypertrophic, restrictive), cardiac arrest (myocardial infarction), cor pulmonale, coronary atherosclerosis, edema, endocarditis (acute bacterial, prosthetic valvular, right-sided, infective), hemorrhage, mitral valve prolapse syndzome, murmur, paricarditis, shock (hypovolemia, vasodilation, septic, cardiogenic), stenosis.

(page 7, line 34 to page 8, line 11). Here, the specification teaches that "Cardiac Response" comprises "activities, alterations and physiological occurrences" in the heart, "or otherwise associated with the heart or the heart's function", which take place during any alteration of the heart. However, the specification does not define or teach what is considered to be "activities, alterations and physiological occurrences in the heart", or what is encompassed by activities, alterations and physiological occurrences "otherwise associated with the heart or the heart's function". At best, the specification teaches that "cardiac response" is not limited to the over 20 distinct conditions listed.

The specification also states, "[t]he heart is architecturally complex and composed of many unique cell types. Heart-affecting effector agents may exclusively affect just one of these cell types, or, more commonly, may interfere with several types simultaneously. Thus, affected areas may range from highly focal to diffuse lesions, and may spread or refocus over time." (page 2, lines 15-19) Here, the specification is stating that "cardiac response" can occur in one of the many unique cells of the heart, or in several cell types simultaneously. This broadens the

scope of what is considered to be a "cardiac response", since this includes analyzing not only single cell types, but multiple cell types simultaneously.

With respect to detecting "CRPI-1", it is not clear as to what protein is being detected. The specification teaches that "CRPI" refers to

> [A] protein isoform that is differentially present in a sample from a subject having a Cardiac Response compared with a sample from a subject free from any Cardiac Response or that is differentially present in a sample from a subject having one or more particular Cardiac Response compared with a sample from a subject free from such one or more particular Cardiac Response or having a distinct Cardiac Response. As used herein, a CRPI is "differentially present" in a first sample with respect to a second sample when a method for detecting the said feature... gives a different signal when applied to the first and second samples...A CRPI is characterized by one or more peptide sequences of which it is comprised...the CRPI may correspond to the previously-identified protein, be a variant of the previously identified protein, or be a previously unknown protein.

(see page 9, line 17 to page 10, line 11). Thus, CRPI-1could encompass any one or more peptide sequences of which it is comprised; it may correspond to a previously identified protein, a variant of the previously identified protein, or be a previously unknown protein. Furthermore, on page 45, Table IX, the specification shows that CRPI-1 has both a rat/mouse accession number and a human homologue accession number, and that CRPI-2 has the same rat/mouse accession number and a human homologue accession number as CRPI-1. Therefore, it is not clear as to what specific protein is meant when referring to CRPI-1.

Accordingly, the claims are broadly drawn to methods for screening, diagnosis or prognosis of *any* "Cardiac Response" in a subject, for determining the stage or severity of *any* "Cardiac Response" in a subject, and for identifying a subject at risk of developing *any* "Cardiac Response" by detecting "CRPI-1" in sample of serum from a subject.

(2) ***Relative Skill of those in the Art, State of the Prior Art, Amount of Direction or Guidance Presented & Presence or Absence of Working Examples***

The specification teaches an experiment of identifying CRFs differentially expressed in the blood, following a "cardiac response" (see pages 102-119). The specification teaches that "cardiac response" was induced by treatment with doxorubicin either alone or 30 mins. after an i.p. injection of dexrazoxane. (See page 103, lines 7-9) The treatment comprised of 7 weekly injections and samples were taken within 24h of after the final injection. (See page 103, lines 10-11)

The specification teaches doxorubicin is a marketed anthracycline anticancer drug that causes a serious chronic cardiac toxicity; a spontaneous hypertensive rat is a useful animal model to study this toxicity; by incorporating a cardioprotectant in the study design, the association of protein markers with the undesirable cardiotoxicity of the cardiotoxic agent is strengthened, and that pretreatment of dexrazoxane provides significant cardioprotection against clinical doxorubicin-induced cardiotoxicity (dexrazoxane has been FDA approved for this indication). (See page 103, lines 13-20)

The specification also teaches the extensive sample preparation, gel preparation, staining, imaging of the gel, and the significant processes for analyzing the sample including digital analysis, assignment of pI and MW, selection of the "primary master image", facilitation of statistical analysis, construction of digital profiles, statistical analysis of the profiles, and the recovery and differential expression analysis of selected profiles. (See pages 103-114)

The specification teaches of most highly preferred differentially expressed CRFs with a p-value less than or equal to 0.001; highly preferred differentially expressed CRFs with a p-value

less than or equal to 0.01, and preferred differentially expressed CRFs with a p-value less than or equal to 0.05. (See tables XII(a-c) on pages 114-118).

In the instant case, the specification teaches:

CRF	PI	MW (Da)	DX vs. Control	P-Value, DX vs. Control
1	5.6	37,430	-23.14	0.021

Thus, the results show there was a 23.14 fold decrease in abundance of CRF-1. Furthermore, on page 29, Table V, the specification shows that CRPI-1 is decreased in blood of subjects having cardiac response.

Accordingly, the specification teaches CRPI-1 is decreased in the blood of subjects being subjected to doxorubicin treatment.

However, the specification does not provide any guidance as to how this information can be used to carry out the broadly claimed methods for screening, diagnosis or prognosis of *any* "Cardiac Response" in a subject, for determining the stage or severity of *any* "Cardiac Response" in a subject, and for identifying a subject at risk of developing *any* "Cardiac Response" by detecting *any* "CRPI-1" in sample of serum from a subject.

The prior art of Coucek et al. (J Mol. Cell Cardiol. (1999) 31:1435-1446) teaches that the administration of doxorubicin affects cardiac gene expression, and has both immediate and persistent effects on cardiac gene expression. (See abstract and pages 1442-1443) Coucek teaches that "the significance of anthracycline-induced effects on cardiac gene expression and the persistent activation of ventricular ANP expression is not known at this time." (See page

1444). Accordingly, Coucek teaches that expression analysis, following the administration of doxorubicin, at best, serves as a basis for further experimentation.

The art of Thompson et al. (Toxological Sciences (2003) 72(S-1): 286, which includes inventors Herman, Zhang and Sistare of the instant invention) also teaches that following the administration of doxorubicin and subsequent gene expression analysis, further experimentation must be conducted. Thompson teaches, "doxorubicin is a cardiotoxic anti-neoplastic drug that induces diffuse cardiac pathology characterized by myofibrillar loss and cytoplasmic vacuolization". (See page 286) Thus, Thompson teaches that the administration of doxorubicin has a specific effect on a sample and would not be considered to cause *any* "cardiac response". Thompson teaches the experiment comprising treating rats with doxorubicin with or without pretreatment of dexrazoxane, and then measuring gene expression for up or down regulation. (See page 286) Furthermore, Thompson teaches dexrazoxane pretreatment modulated doxorubicin–induced decreases in some genes involved in heart function. (See page 286) Thompson concludes by stating, "these genes *may* provide mechanistic clues for the rational design of clinical strategies to further reduce doxorubicin cardiotoxicity." (emphasis added by Examiner, See page 286) Therefore, Thompson teaches the administration of doxorubicin has a specific effect on a sample (i.e., induces diffuse cardiac pathology characterized by myofibrillar loss and cytoplasmic vacuolization), and that following doxorubicin treatment, gene expression analysis serves as a starting point for experimentation to determine a "rational design of clinical strategies to further reduce doxorubicin cardiotoxicity". Accordingly, Thompson teaches that gene expression analysis, following doxorubicin treatment, at best, provides a basis for further experimentation.

Given the teachings of the prior art, and the lack of examples of carrying out the claimed methods, the level of skill in the art is high.

(3) ***Quantity of Experimentation Necessary & the Unpredictability of the Art***

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. In *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art.

In the instant case, the art nor the specification teaches the association and/or correlation of the detection of *any* "CRPI-1" protein and *any* "cardiac response", and therefore, the specification not teach does the skilled artisan how to use "CRPI-1" in, for example, a method of diagnosing an irregular heartbeat.

In order to carry out making and using "CRPI-1", the experimentation required by the skilled artisan would be considered undue. First, the skilled artisan would have to determine what is encompassed by "CRPI-1", this could be any one of a number of proteins given the description of what might be encompassed by the recitation of "CRPI-1" (see above). Once the artisan determined all of the possible "CRPI-1" proteins, the artisan would have to determine what is encompassed by "cardiac response" (see above for discussion on the breadth of what might be considered as a "cardiac response"). There is little guidance in the specification for such determinations. Then, in order to acquire statistically significant evidence of an association

with a "CRPI-1" protein and the diagnosis or prognosis of *any* "cardiac response", determining the stage or severity of *any* "Cardiac Response" in a subject, and for identifying a subject at risk of developing *any* "Cardiac Response" by detecting *any* "CRPI-1" in sample of serum from a subject, dozens of patients in each of the many hundreds of different possible "cardiac responses" would need to be subjected to collection of samples for analysis of their expression profiles, followed by analysis and the inventive efforts of determining if any association exists. This is a very large quantity of experimentation, especially in light of the lack of guidance given by the specification as to any association of the "CRPI-1" and any condition or disease. Overall, such experimentation requires an immense amount of trial and error analysis, with little to no starting point, absent any teaching in the specification, wherein the results of such analysis are unpredictable, and is therefore considered undue.

In essence, the experimentation that one skilled in the art would be required to perform is in fact the proposed novelty of the invention. However, "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". (*Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001).

Accordingly, due to the breadth of the claims, the large quantity of experimentation, the lack of direction/guidance presented in the specification, the absence of working examples directed to using any "CRPI-1" protein, the complex nature of the invention, the further experimentation needed as suggested in the art, the extreme unpredictability of the invention, and the high level of skill in the art, undue experimentation would be required of the skilled artisan to use the claimed invention in its full scope.

Conclusion

13. No Claims are allowable.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (571) 272-0788. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Carla Myers, can be reached at (571) 272-0747. If attempts to reach Carla Myers are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (571) 272-0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Alexander H. Spiegler
June 14, 2004

CARLA J. MYERS
PRIMARY EXAMINER